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PATENT SPECIFICATION

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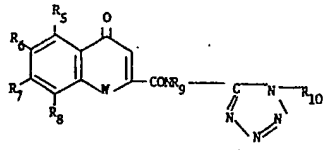
(19)

(54) CHROMONE AND THIACHROMONE CARBOXYAMIDO TETRAZOLES

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new 4-oxo-4H-1-benzopyran and 4-oxo-4H-1-thiobenzopyran derivatives, compositions containing them and methods for their preparation.

According to our invention we provide compounds of formula I,

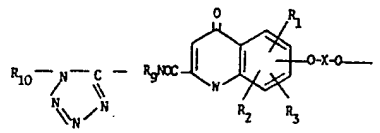


I

in which R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, alkyl, halogen, hydroxy, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy or phenylalkoxy; the alkyl, alkenyl, phenyl, alkoxy, alkenyloxy and phenylalkoxy groups optionally being substituted by a hydroxy, alkoxy, or halo group or by a heterocyclic ring containing carbon and oxygen,

or an adjacent pair of R_5, R_6, R_7 and R_8, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

or one of R_5, R_6, R_7 and R_8 represents a group of formula XXI,



XXI

in which R_1, R_2, R_3 have the same significances as R_5, R_6, R_7 and R_8 above, save that they do not represent a group of formula XXI and that an adjacent pair of R_1 to R_3 do not, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

X is a saturated or unsaturated, substituted or unsubstituted, straight or branched hydrocarbon chain which may be interrupted by a carbocyclic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups,

each pair of R_9 and R_{10} may be the same or different, and

R_9 and R_{10} are the same or different, and are hydrogen, alkyl Cl to 6, alkenyl C2 to 6, phenyl-(alkyl Cl to 6), alkanoyl C2 to 6 or alkoxy carbonyl C2 to 6, and

W is oxygen or sulphur,

provided that when R_9 and R_{10} are both hydrogen, R_5, R_6, R_7 and R_8 do not represent a group of formula XXI and W is oxygen, then

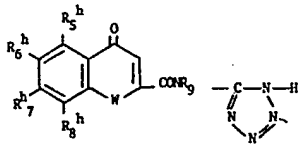
(i) 3 or 4 or R_5, R_6, R_7 and R_8 are other than hydrogen, or

(ii) at least one of R_5, R_6, R_7 and R_8 represent alkenyl, phenyl or alkenyloxy; or an alkyl, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy or phenylalkoxy group each of which is substituted by a halo group or by a heterocyclic ring containing carbon and oxygen; or an alkyl, alkenyl, phenoxyalkoxy, phenylalkoxy or phenyl group each of which is substituted by a hydroxy or alkoxy group,

and pharmaceutically acceptable salts thereof.

According to our invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable salt thereof, which comprises

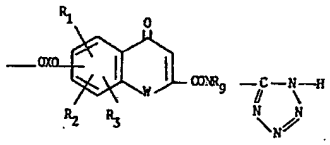
(a) producing a compound of formula Ia,



Ia

in which W and R_9 are as defined above, and

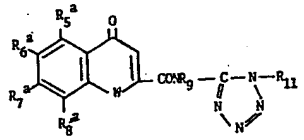
R_5^h, R_6^h, R_7^h and R_8^h have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^h, R_6^h, R_7^h and R_8^h may represent a group of formula XXII,



XXII

in which X, R_1, R_2, R_3, W and R_9 are as defined above,

by replacing a group R_{11} with hydrogen in a compound of formula II,

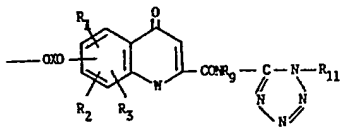


II

in which R_9 and W are as defined above, and

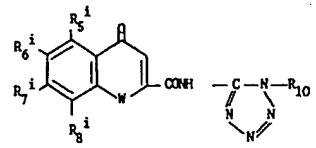
R_{11} represents an aralkyl, an aroylalkyl, an acyloran amino group, or a group $-(CH_2)_2G$ is which G is an electron withdrawing group, and

R_5^a, R_6^a, R_7^a and R_8^a have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^a, R_6^a, R_7^a and R_8^a may represent a group of formula III,



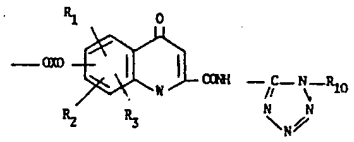
III

in which R_1, R_2, R_3, X, R_9 and R_{11} are as defined above,
(b) producing a compound of formula Ib,



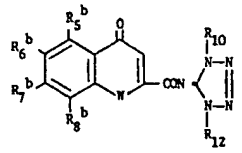
Ib

in which W and R_{10} are as defined above, and
R_5^i, R_6^i, R_7^i and R_8^i have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^i, R_6^i, R_7^i and R_8^i may represent a group of formula XXIII,



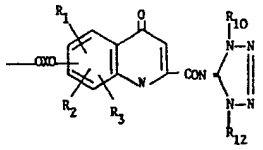
XXIII

in which X, R_1, R_2, R_3, W and R_{10} are as defined above, by
(i) replacing a group R_{12} with a hydrogen in a compound of formula IV,



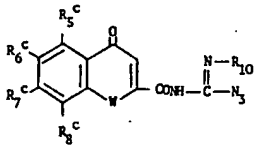
IV

in which W and R_{10} are as defined above,
R_{12} has the same significance as R_{11}, and
R_5^b, R_6^b, R_7^b and R_8^b have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^b, R_6^b, R_7^b and R_8^b may be a group of formula V,



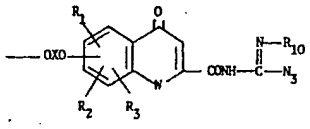
V

in which X, R_1, R_2, R_3, W, R_{10} and R_{12} are as defined above,
(ii) cyclising a compound of formula VI,



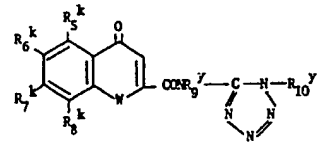
VI

in which W and R_{10} are as defined above, and
R_5^c, R_6^c, R_7^c and R_8^c have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^c, R_6^c, R_7^c and R_8^c may represent a group of formula VII,



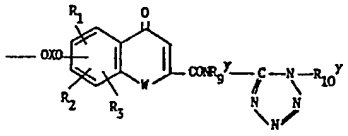
VII

in which X, R_1, R_2, R_3, W and R_{10} are as defined above,
(c) producing a compound of formula Ic,



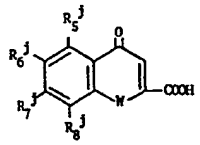
Ic

in which W and the proviso are as defined above,
R_5^k, R_6^k, R_7^k and R_8^k have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^k, R_6^k, R_7^k and R_8^k may represent a group of formula XXV,



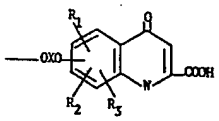
XXV

in which R_1, R_2, R_3, W and X are as defined above, and
R_9^y and R_{10}^y have the same significances as R_9 and R_{10} above, save that R_9^y must be hydrogen when R_{10}^y is hydrogen, by reacting a compound of formula VIII,



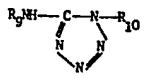
VIII

in which W and the proviso are as defined above, and
R_5^j, R_6^j, R_7^j and R_8^j have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^j, R_6^j, R_7^j and R_8^j may represent a group of formula XXIV,



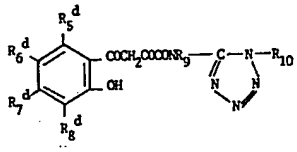
XXIV

in which X, R_1, R_2, R_3 and W are as defined above,
or an acid halide, an ester or a mixed anhydride thereof, with a compound of formula IX,



IX

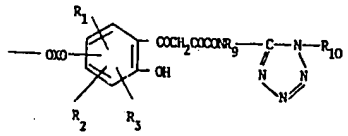
in which R_9 and R_{10} are as defined above,
(d) producing a compound of formula I in which W is oxygen by cyclising a compound of formula X,



X

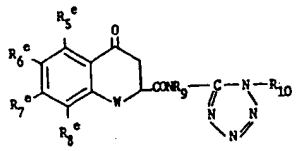
or an alkali metal salt thereof,

in which R_9 and R_{10} are as defined above, and
R_5^d, R_6^d, R_7^d and R_8^d have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^d, R_6^d, R_7^d and R_8^d may represent a group of formula XI,



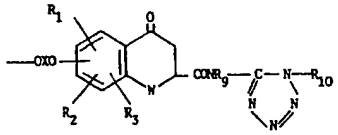
XI

in which R_1, R_2, R_3, X, R_9 and R_{10} are as defined above,
or (e) selectively dehydrogenating a compound of formula XII,



XII

in which W, R_9 and R_{10} are as defined above, and
R_5^e, R_6^e, R_7^e and R_8^e have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^e, R_6^e, R_7^e and R_8^e may represent a group of formula XIII,



XIII

in which R_1, R_2, R_3, X, W, R_9 and R_{10} are as defined above,
and where desired or necessary converting the compound of formula I to a pharmaceutically acceptable salt thereof.

In process (a) the group R_{11} may be an aralkyl, e.g. a benzyl, *p*-methoxybenzyl, triphenylmethyl or diphenylmethyl group; an aroylalkyl, e.g. a phenacyl group; an acyl, e.g. acetyl group; an amino group; or a group $-(CH_2)_2G$, where G is an electron withdrawing group, for example a nitrile, a carboxylic ester, e.g. a lower alkanol, or an acyl group, e.g. an acetyl group.

When R_{11} represents an aralkyl group the group may be removed either using a hydrogen halide, e.g. HBr, in acetic acid or by catalytic hydrogenation using, for example, a palladium catalyst in a solvent which is inert under the reaction conditions, e.g. acetic acid, or by using sodium in liquid ammonia.

When R_{11} represents an acyl or a $-CH_2CH_2G$ group, the group may be removed under basic conditions with, for example, sodium hydroxide.

When R_{11} represents an amino group, the group may be removed by reductive de-amination with, for example, hypophosphorous acid, stannous chloride or sodium in liquid ammonia.

Process (b)(i) may be carried out under the same conditions as specified above for process (a).

R_{12} should not of course be the same as R_{10}.

Process (b)(ii) may be carried out under basic conditions, e.g. by treating the compound of formula VI with a mild base such as sodium bicarbonate. Alternatively the cyclisation may be effected at an elevated temperature, for example of from 50 to 150°C, preferably in a solvent which is inert under the reaction conditions, e.g. dimethylformamide.

In process (c) the anhydride is preferably a mixed anhydride of such a type that it will cleave preferentially, to give the desired benzopyran-carboxamidotetrazole, as the major product when reacted with a compound of formula IX. Examples of suitable acids from which the mixed anhydride may be derived are sulphonic acids, e.g. benzene sulphonic acid, sterically hindered carboxylic acids, e.g. pivalic, isovaleric, diethylacetic or triphenylacetic acid, and alkoxy formic acids, e.g. ethoxy or isobutoxy formic acid. The reaction is preferably carried out

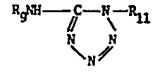
under anhydrous conditions in a solvent which will not react with either the compound of formula IX or the mixed anhydride, e.g. pyridine or dimethylformamide. However when the reaction is carried out in a non-basic solvent, e.g. dimethylformamide, an adequate porportion of an acid acceptor, e.g. triethylamine, should also preferably be present. The reaction is preferably carried out at a temperature of from about −15° to +20°C. When an acid halide is used it may conveniently be an acid chloride. When an ester is used we prefer to use a lower alkoxy ester and carry out the reaction in a solvent which is inert under the reaction conditions, e.g. glacial acetic acid, at a temperature of from about 100 to 200°C. When a compound of formula VIII itself is used the reaction may be carried out by heating the compound of formula VIII and the compound of formula IX in a solvent which is inert under the reaction conditions, e.g. dimethylacetamide, at a temperature of from 100 to 200°C. Alternatively the reaction may be carried out in the presence of a condensation agent, e.g. N,N'-carbonyldiimidazole or dicyclohexyl carbodiimide, in an aprotic solvent, e.g. dimethylformamide, at a temperature of from about 10 to 40°C.

In process (d) the cyclisation may be carried out by heating or under basic or neutral conditions. It is however, preferred to carry out the cyclisation in the presence of an acid, e.g. hydrochloric acid, and in a solvent which is inert under the reaction conditions, e.g. ethanol or dimethylacetamide. The reaction may be carried out at a temperature of from 20 to 150°C.

In process (e) the dehydrogenation may be carried out using a mild oxidising agent, e.g. selenium dioxide or chloranil. Alternatively the dehydrogenation may be carried out indirectly by halogenation followed by dehydrohalogenation, for example by treatment with N-bromosuccinimide or pyridinium bromide perbromide to yield the 3-bromo derivative, which is subsequently dehydrobrominated. The reaction may be carried out in a solvent which is inert under the reaction conditions, e.g. a halogenated hydrocarbon such as chloroform, xylene or glacial acetic acid. The reaction may be carried out at a temperature of from about 20° to 150°C.

The compounds of formula I may be recovered from the reaction mixture using conventional techniques.

The compounds of formula II may be made by reaction of an acid halide or a mixed anhydride of a compound of formula VIII with a compound of formula XIV,

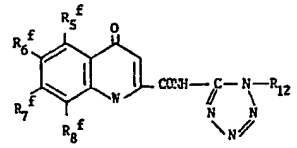


XIV

in which R_9 and R_{11} are as defined above. The reaction may be carried out under the conditions set out for process (c) above.

The acid halides and the mixed anhydrides of the compounds of formula VIII, the compounds of formula III themselves, and the compounds of formulae IX and XIV are either known or may be made by methods known for the manufacture of similar known compounds.

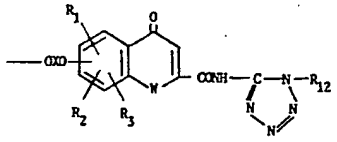
The compounds of formula IV may be made by reacting a compound of formula XV,



XV

in which W and R_{12} are as defined above, and

R_5^f, R_6^f, R_7^f and R_8^f have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^f, R_6^f, R_7^f and R_8^f may be a group of formula XVI,



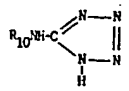
XVI

in which X, R_1, R_2, R_3 and R_{12} are as defined above,

with a compound $R_{10}Hal$ in which Hal represents a halogen atom and R_{10} is as defined above. The reaction may be carried out by reacting the compound of formula XV with sodium hydride in hexamethylphosphoramide as solvent, and then adding the compound $R_{10}Hal$, e.g. methyliodide with stirring at room temperature. Alternatively, when R_{10} is methyl, the compound of formula XV may be reacted with diazomethane in a solvent such as dimethylformamide.

The compounds of formula XV may be made from compounds of formula VIII by processes analogous to process (c) above.

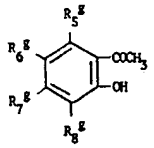
The compounds of formula VI may be made by reacting an acid halide of a compound of formula VIII with a compound of formula XVII,



XVII

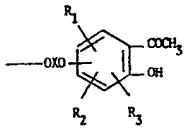
in which R_{10} is as defined above. The reaction may be carried out in a suitable solvent which is inert under the reaction conditions and in the presence of an acid acceptor, e.g. triethylamine in dimethylacetamide. Alternatively the reaction may be carried out in a basic solvent, e.g. pyridine.

Compounds of formula X may be made by reacting a compound of formula XVIII,



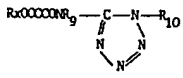
XVIII

in which R_5^g, R_6^g, R_7^g and R_8^g have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^g, R_6^g, R_7^g and R_8^g may represent a group of formula XIX,



XIX

in which R_1, R_2, R_3 and X are as defined above,
with a compound of formula XX,



XX

in which R_9 and R_{10} are as defined above, and

Rx is an alkyl Cl to 6 group. The reaction may be carried out under conditions conventional for a Claisen condensation.

Compounds of formula X may also be prepared by the action of mild alkali on a compound of formula I.

Compounds of formula XII may be made by selective hydrogenation of a compound of formula I or by a method analogous to process (c) above using an appropriate chromanone-2-carboxylic acid, or an acid halide, an ester or a mixed anhydride thereof.

Compounds of formulae XVIII and XX are either known or may be made from known compounds using techniques known *per se*.

Some of the groups R_5, R_6, R_7, R_8, R_1, R_2, R_3 and X may be affected by the reaction conditions described above. Where necessary or desirable therefore the reaction may be carried out using protected derivatives of the reagents, for example —OH groups may be protected by formylation.

The processes described above may produce a compound of formula I or a salt thereof. It is also within the scope of this invention to treat any salt so

produced to liberate the free compound of formula I, or to convert one derivative into another. Suitable salts include water-soluble salts. Salts which may be mentioned include salts with inorganic alkalis, such as the alkali-metal and alkaline-earth metal salts e.g. the potassium, lithium and calcium salts and, notably the sodium salt. Other salts include salts with organic bases, e.g. bases containing both nitrogen and oxygen atoms. Specifically there may be mentioned salts with alkanolamines, e.g. tri- and di-ethanolamine; hydroxyalkylalkylamines, e.g. tri-(hydroxymethyl) methylamine; 5 or 6 membered nitrogen containing heterocyclic rings, e.g. morpholine; and N-alkylamino substituted sugars, e.g. N-methyl-glucamine.

According to a further feature of our invention we provide a process for the production of a pharmaceutically acceptable salt of a compound of formula I, which comprises treating a compound of formula I or another salt thereof, with a compound containing an available pharmaceutically acceptable cation, e.g. by treating the compound of formula I with a base, or with an appropriate salt using a metathetical process.

The —CONH— group in the compounds of formula Ib may exist in the tautomeric form —C(OH)=N—. Other tautomeric forms are also contemplated,

The compounds of formula I, and pharmaceutically acceptable salts thereof, are useful because they possess pharmacological activity in animals; in particular they are useful because they inhibit the release and/or action of pharmacological mediators which result from the *in vivo* combination of certain types of antibody and specific antigen, e.g. the combination of reaginic antibody with specific antigen. (See Example A below).

In man, both subjective and objective changes which result from the inhalation of specific antigen by sensitised subjects are inhibited by prior administration of the new compounds. Thus the new compounds are indicated for use in the treatment of asthma, e.g. allergic asthma. The new compounds are also indicated for use in the treatment of so-called 'intrinsic' asthma (in which no sensitivity to extrinsic antigen can be demonstrated). The new compounds are also indicated for use in the treatment of other conditions in which antigen-antibody reactions are responsible for disease, for example, hay fever, certain eye conditions, e.g. trachoma; urticaria; and gastrointestinal allergy, especially in children, e.g. milk allergy.

For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 0.1 to 50 mg per kg of animal body weight in the test set out in Example A. For man the total daily dosage is in the range of from about 1 mg to 3,500 mg which may be administered in divided doses from 1 to 6 times a day or in sustained release form. Thus dosage forms suitable for administration (by inhalation or oesophageally) comprise from about 0.17 mg to 600 mg of the compound admixed with a solid or liquid pharmaceutically acceptable diluent or carrier.

According to our invention we also provide a pharmaceutical composition comprising (preferably a minor proportion of) a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of suitable adjuvants, diluents or carriers are:— for tablets and dragées; lactose, starch, talc or stearic acid; for capsules, tartaric acid or lactose; for suppositories and ointments, natural or hardened oils or waxes; for inhalation compositions, coarse lactose. For use in inhalation compositions the compounds of formula I, or the pharmaceutically acceptable salt thereof, preferably has a fine particle size of from 0.01 to 10 microns and may if desired be used in combination with a bronchodilator, e.g. isoprenaline. The compound of fine particle size may be made, for example by grinding or milling. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilisers, sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form. Compositions for inhalation may also comprise a solution, e.g. an aqueous solution, of the compound of formula I or the pharmaceutically acceptable salt thereof; or may comprise a mixture of the compound with the liquifiable gas, under pressure, the mixture being put up in a container having a valve adapted to dispense a metered dose.

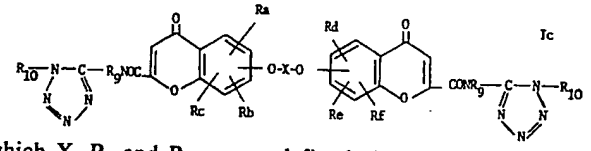
In compounds of formula I it is preferred that R_5, R_6, R_7 and R_8 should each

contain less than 8 carbon atoms, or that one of R_5, R_6, R_7 and R_8 should represent a group of formula XXI.

As specific values of R_1, R_2, R_3, R_5, R_6, R_7 and R_8 there may be mentioned ethyl, chloro, allyl, ethoxy, allyloxy, benzyloxy, hydroxypropoxy, ethoxy-ethoxy, or alkoxy substituted by a 5 or 6 membered heterocyclic ring containing carbon and oxygen, e.g. tetrahydrofurfuryloxy, and chlorophenoxyethoxy.

We prefer those compounds in which R_9 and R_{10} are both hydrogen, or R_9 and R_{10} are different, one being hydrogen and the other being other than hydrogen, e.g. alkyl Cl to 6 or phenyl-(alkyl Cl to 6). Specific values of R_9 and R_{10} which may be mentioned are hydrogen, methyl, benzyl, allyl, acetyl and ethoxycarbonyl.

As a specific group of compounds we provide those of formula Ic,



Ic

in which X, R_9 and R_{10} are as defined above, and

Ra, Rb, Rc, Rd, Re and Rf are the same or are different and each is a hydrogen or halogen atom or an alkyl, hydroxy, alkenyl, alkenyloxy, alkoxy, hydroxyalkoxy or alkoxyalkoxy group.

In general, it is preferred that nor more than one of Ra, Rb and Rc and not more than one of Rd, Re and Rf is other than hydrogen.

Particularly preferred compounds according to the invention are those in which all of Ra, Rb, Rc, Rd, Re and Rf are hydrogen.

The group X may be any of a wide variety of groups. Thus, for example, it may be a substituted or unsubstituted, straight or branched, saturated or unsaturated hydrocarbon chain. Further, X may be such a chain interrupted by one or more oxygen atoms, carbonyl groups or by a carbocyclic or hetercyclic ring and may be substituted by one or more halogen atoms (e.g. chlorine or bromine atoms) or hydroxy or alkoxy groups. Specific examples of the group X are groups of the formulae:—

$$-(CH_2)_3-$$

$$-(CH_2)_5-$$

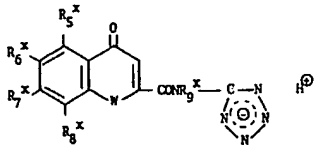
$$-CH_2CHOHCH_2-$$

$$-CH_2CH_2CHOHCH_2CH_2-$$

The group X is preferably a substituted or unsubstituted straight or branched hydrocarbon chain, which may be interrupted by one or more oxygen atoms, and contains from 3 to 7 carbon atoms. Desirably such a chain is substituted by one or more hydroxyl groups; a particularly preferred chain being the 2-hydroxy-trimethylene chain ($-CH_2CHOHCH_2-$).

In compounds of formula Ic we prefer the —OXO— group to link the benzopyran nuclei in the 5 and 5' positions.

As a further specific group of compounds we provide those of formula Id,



Id

in which R_5^x, R_6^x, R_7^x and R_8^x which may be the same or different, each represent hydrogen, alkyl, halogen, hydroxy, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy or phenylalkoxy; the alkyl, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy and phenylalkoxy groups optionally being substituted by a hydroxy, alkoxy or halo group or by a heterocyclic ring containing carbon and oxygen,

or an adjacent pair of R_5, R_6, R_7 and R_8, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

R_9^x is hydrogen or lower alkyl,

and the proviso is as defined with respect to formula I.

The invention is illustrated, but in no way limited by the following Examples.

Example 1.

1-Methyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole.

4-Oxo-4H-1-benzopyran-2-carbonyl chloride (2.7g), 5-amino-1-methyltetrazole (1.3g) and dry triethylamine (3.5 ml) were dissolved in dry N,N-dimethylacetamide (50 ml) and the reaction mixture was stirred at 21°C for 2¼ hours. The mixture was then cooled and the triethylamine hydrochloride was filtered off. The filtrate was evaporated to dryness to yield a light brown solid, which was triturated with 10% aqueous sodium bicarbonate solution, finally washed with water and dried *in vacuo*, (3g). The 1-methyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole was purified by crystallisation from acetic acid-water. The crystalline solid was dried *in vacuo*, (1.2g); mp 255—256°C.

Analysis

	Found:	C, 53.0;	H, 3.4;	N, 25.6%
$C_{12}H_9N_5O_3$	Requires:	C, 53.1;	H, 3.4;	N, 25.8%

Spectral Confirmation

The nmr spectrum in hexadeuterodimethylsulphoxide displayed a three proton, singlet resonance at 5.96τ for the N-1-methyl group and a one proton, singlet resonance at 2.94τ for the 3-proton. The molecular weight of 271 was confirmed by mass spectroscopy.

Example 2.

1-Benzyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole.

4-Oxo-4H-1-benzopyran-2-carbonyl chloride (10.4g), 5-amino-1-benzyltetrazole (12.1g) and dry triethylamine (12.8 ml) were dissolved in dry N,N-dimethylacetamide (100 ml). The mixture was cooled and the triethylamine hydrochloride was filtered off. The filtrate was evaporated to dryness to give a red oil, which, when triturated with water, afforded a white solid. This was filtered off and dried *in vacuo* (12.0g), mp 195—199°C. The compound was heated with aqueous sodium bicarbonate solution, filtered off, washed with water and dried. Crystallisation from ethanol afforded pure 1-benzyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)-tetrazole, (4.4g), mp 224—226°C.

Analysis

	Found:	C, 61.3;	H, 3.6;	N, 19.8%
$C_{18}H_{13}N_5O_3$	Requires:	C, 62.2;	H, 3.8;	N, 20.0%

Spectral Confirmation

The molecular weight of 347 was confirmed by mass spectroscopy. The nmr spectrum in hexadeuterodimethylsulphoxide revealed a two proton singlet at 4.47τ for the benzylic methylene group and a sharp, one proton, singlet at 2.98τ for the 3-proton.

Example 3.

1-Methyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole.

(a) 4 - Oxo - 4H - 1 - benzopyran - 2 - [N - (1 - benzyl - 4 - methyl - 2 - tetrazolin - 5-ylidene)]carboxamide.

1-Benzyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole, (7.0g) was dissolved in dry hexamethylphosphoramide (100 ml). Sodium hydride (1.14g : 50% dispersion in mineral oil) was added and when all evolution of hydrogen had ceased, methyl iodide (10 ml) was added and the mixture was stirred for 18 hours at 21°C. The reaction mixture was poured into water (1,000 ml) and the resulting oil was extracted into ethyl acetate. The organic layer was separated, washed with water, dried over magnesium sulphate, filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was crystallised from ether to give 4-oxo-4H-1-benzopyran-2-[N-(1-benzyl-4-methyl-2-tetrazolin-5-ylidene)]carboxamide (4.0g) as a white crystalline solid, mp 140—141°C.

Spectral Confirmation

The molecular weight of 361 was confirmed by mass spectroscopy. The nmr spectrum in deuterochloroform revealed a three proton singlet resonance at 6.03τ for the methyl group; a two proton singlet at 4.48τ for the benzylic methylene group; a one proton singlet at 2.74τ for the 3-proton; a five proton singlet at 2.64τ for the benzyl group and a series of multiplets between 2.5 and 1.7τ for the four

aromatic protons of the chromone moiety. The infra red spectrum displayed intense bands at 1655 and 1640 cm^{-1}.

(b) 1 - Methyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole.

4 - Oxo - 4H - 1 - benzopyran - 2 - [N - (1 - benzyl - 4 - methyl - 2 - tetrazolin - 5-ylidene)]carboxamide (4.0g) was dissolved in glacial acetic acid (200 ml). 10% Palladium on charcoal catalyst (0.4g) was added to the solution and the mixture was hydrogenated at 45 p.s.i. for 24 hours at 21°C. The reaction mixture was filtered to remove the catalyst and the filtrate was evaporated to dryness *in vacuo* to yield a yellow solid. This material was crystallised from methanol to give a solid (0.2g). The latter was dissolved in sodium bicarbonate solution and the resulting sodium salt of the desired compound crystallised out. The crystalline solid was dissolved in water, acidified to pH 1 concentrated hydrochloric acid and the resulting precipitate of 1-methyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole was filtered off washed with water and dried *in vacuo* to give a white solid (0.2g), mp 255—256°C. No depression of melting point occurred on admixture with authentic material, prepared by the method of Example 1.

Spectral Confirmation

The infra red spectrum was superimposeable with that of authentic 1-methyl-5-(4-oxo-4H-1-benzopyran-2-carboxamido)tetrazole.

Example 4.

5-[8-Allyl-5-(3-methylbutoxy)-4-oxo-4H-1-benzopyran-2-carboxamido]tetrazole.

(a) 5 - [8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole.

8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carbonyl chloride (33.5g; 0.10 mole) and anhydrous 5-aminotetrazole (9.3g; 0.11 mole) were mutually dissolved in dry pyridine (125ml). The resulting solution, which initially became warm, was heated on a steam bath overnight. The reddish brown mixture was evaporated to dryness and the residual oil was triturated with dilute hydrochloric acid to give a brownish solid, which was collected, washed with water and dried *in vacuo* (34g). Crystallization from methanol afforded pure 5 - [8 - allyl-5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole (14g), mp 204—206°C (decomp).

Analysis: Found: C, 59.8; H, 5.6; N, 18.1%
$C_{19}H_{21}N_5O_4$ requires: C, 59.5; H, 5.5; N, 18.3%

Special Confirmation

The molecular weight of 383 was confirmed by mass spectroscopy. The nmr spectrum in hexadeuterodimethylsulphoxide revealed a sharp singlet resonance for the 3-proton of the benzopyran ring system at 3.05τ. The i.r. spectrum displayed peaks at 3250 cm^{-1} and 1695 cm^{-1} for the NH (str) and amide I band respectively.

(b) 5 - [8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole sodium salt.

5 - [8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole (11.2g; 0.029 mole), sodium bicarbonate (2.48g; 0.029 mole) and water (320ml) were heated on a steam bath until dissolution was complete. On cooling 5 - [8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2-carboxamido]tetrazole sodium salt hemihydrate began to crystallize as white plates, which were collected and dried *in vacuo* (9.1g).

Analysis: Found: C, 55.0; H, 5.1; N, 16.9%
$C_{19}H_{20}N_5NaO_4.\frac{1}{2}H_2O$ requires: C, 55.1; H, 5.0; N, 16.9%

Spectral Confirmation

The i.r. spectrum displayed the amide I band at 1650 cm^{-1}. The nmr spectrum in hexadeuterodimethylsulphoxide revealed a sharp singlet resonance for the 3-proton of the benzopyran ring at 3.3τ.

Example 5.

5 - [2 - (4 - Chlorophenoxy)ethoxy] - 4 - oxo - 8 - n - propyl - 4H - 1 - benzopyran - 2-carboxamido]tetrazole.

(a) 2-(4-Chlorophenoxy)ethyl methansulphonate.

To a stirred solution of 78.2 parts of 2-(4-chlorophenoxy)ethanol and 57.2

parts of methanesulphonyl chloride in 350 parts of diethyl ether, cooled to –15°C, was added, over a period of 30 minutes, 55 parts of dry pyridine. Cooling was removed and the mixture was then stirred at room temperature for 17 hours, then it was successively extracted with 200 parts of water, 150 parts of 2 Normal hydrochloric acid, 50 parts of water, 2 lots of 75 parts of 3% sodium bicarbonate solution and finally with 50 parts of water. The ethereal solution was then dried over anhydrous magnesium sulphate, filtered and evaporated to half bulk. The solution on standing deposited white crystals which were filtered off and dried to leave 34.8 parts of 2-(4-chlorophenoxy)ethylmethane sulphonate, melting point 70—76°C. The structure was confirmed by nuclear magnetic resonance spectroscopy. ($CDCl_3$) centres about 3.01 (4H, AA', BB' p-disubd.ring protons): centred about 5.67 (4H, $—CH_2.CH_2—$, A_2B_2); 6.98 (3H, $CH_3—$, singlet).

(b) 6-[2-(4-Chlorophenoxy)ethoxy]-2-hydroxy-3-n-propylacetophenone.

To a stirred solution of sodium ethoxide prepared by dissolving 3.15 parts of sodium in 120 parts of ethanol was added 26.4 parts of 2,6-dihydroxy-3-n-propylacetophenone. This solution was then added over 15 minutes to a stirred solution of 34.6 parts of 2-(4-chlorophenoxy)ethyl methanesulphonate in 120 parts of ethanol and the final mixture was then stirred and heated under reflux for 18 hours.

The mixture was then allowed to cool and the solid which crystallised was filtered off, washed with a little ethanol, suspended in dilute hydrochloric acid, filtered off, washed with water and dried to leave 30.5 parts of 6 - [2 - (4 - chlorophenoxy)ethoxy] - 2 - hydroxy - 3 - n - propylacetophenone, melting point, 106—107°C.

Analysis:

Molecular weight Found: 348/350 (Mass spectroscopy)
$C_{19}H_{21}ClO_4$ requires: 348.5

(c) 5 - [2 - (4 - Chlorophenoxy)ethoxy] - 4 - oxo - 8 - n - propyl - 4H - 1 - benzopyran-2 - carboxylic acid.

To a stirred solution of sodium ethoxide, prepared by dissolving 11.5 parts of sodium in 280 parts of ethanol, was added a slurry of 30.5 parts of 6 - [2 - (4 - chlorophenoxy)ethoxy] - 2 - hydroxy - 3 - n - propylacetophenone and 36.5 parts of diethyl oxalate in 40 parts of ethanol. The mixture was stirred and heated under reflux for 16 hours then it was cooled and poured into a stirred mixture of 400 parts of 1.5 Normal hydrochloric acid and 240 parts of chloroform. The chloroform layer was isolated, washed with water then evaporated and the residual oil was then treated with 80 parts of ethanol and 5 parts of concentrated hydrochloric acid. The mixture was heated under reflux for 15 minutes and then evaporated. The residue was treated with 12 parts of sodium bicarbonate, 100 parts of water and 120 parts of methanol and the mixture was then heated under reflux for 1.5 hours. Most of the alcohol was then boiled off and the remaining solution ws diluted with 100 parts of hot water. The solution was filtered while hot, cooled and acidified with concentrated hydrochloric acid. A solid was precipitated which was filtered off washed with water and dried to leave a brown solid. The solid was triturated with a mixture of chloroform and diethyl ether, with a mixture of benzene and petrol (bp 60—80°) then with diethyl ether and was then dried thoroughly to leave 21 parts of 5 - [2 - (4 - chlorophenoxy)ethoxy] - 4 - oxo - 8 - n-propyl - 4H - 1 - benzopyran - 2 - carboxylic acid hemi-hydrate, melting point 167—168°C.

Analysis: Found: C, 61.3 ; H, 4.9 ; Cl 8.75
$C_{21}H_{19}ClO_6.\frac{1}{2}H_2O$ requires: C, 61.25: H, 4.86; Cl 8.63%

(d) 5 - (5 - [2 - (4 - Chlorophenoxy)ethoxy] - 4 - oxo - 8 - n - propyl - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole.

A stirred mixture of 15 parts of 5 - [2 - (4 - chlorophenoxy)ethoxy] - 4 - oxo-8 - n - propyl - 4H - 1 - benzopyran - 2 - carboxylic acid, 2 parts of dimethylformamide and 125 parts of 1,2-dichloroethane was treated with 6.5 parts of thionyl chloride. The mixture was stirred and heated under reflux for 16 hours then the solvent was evaporated. A brown solid residue remained which was then dissolved in a solution of 5 parts of anhydrous 5-aminotetrazole in 100 parts of dry pyridine. The new mixture was then stirred and heated under reflux for 1 hour. Most of the pyridine was then evaporated off and the concentrated solution crystallised on

cooling. Crystals were filtered off, washed with a little pyridine, triturated with 80% aqueous ethanol, washed with ethanol and thoroughly dried to leave 8.5 parts of 5 - (5 - [2 - (4 - chlorophenoxy)ethoxy] - 4 - oxo - 8 - n - propyl - 4H - 1-benzopyran - 2 - carboxamido)tetrazole, melting point 232—235°C (decomp.).

Analysis: Found: C, 56.3; H, 4.2 ; N, 14.8
$C_{22}H_{20}ClN_4O_5$ requires: C, 56.3; H, 4.29; N, 14.9%.

(e) Sodium salt.

A mixture of 10.32 parts of 5 - (5 - [2 - (4 - chlorophenoxy)ethoxy] - 4 - oxo - 8-n - propyl - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole, 1.85 parts of sodium bicarbonate, 100 parts of water and 80 parts of methanol was heated to give an almost clear solution which was filtered while hot. Most of the methanol was then evaporated off and the remaining solution was then freeze-dried and further dried *in vacuo* to give 10.1 parts of 5 - (5 - [2 - (4 - chlorophenoxy)ethoxy] - 4 - oxo - 8 - n-propyl - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole, sodium salt.

Analysis: Found: C, 51.4; H, 4.3; N, 13.5
$C_{22}H_{19}ClN_4O_5Na.4.3\%H_2O$ requires: C, 51.4; H, 4.2; N, 13.6%.

Example 6.

5,5' - [(2 - Hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran - 2-carboxamido)tetrazole].

(a) 5,5' - [(2 - Formyloxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran-2 - carboxylic acid].

A suspension of 5,5' - [(2 - hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H-1 - benzopyran - 2 - carboxylic acid] (94g; 0.2 mole) in formic acid (1 litre) was stirred and heated on a steam bath for 18 hours. A white precipitate of the desired product, as its monohydrate, was filtered off, washed with water and dried *in vacuo*, (100g), mp 234—240°.

Analysis: Found: C, 55.6; H, 3.4%
$C_{24}H_{16}O_{12}H_2O$ requires: C, 56.0; H, 3.5%

Spectral Confirmation

The nmr spectrum in hexadeuterodimethylsulphoxide displayed a sharp, singlet resonance at 1.55τ for the formyl proton.

(b) 5,5' - [(2 - Formyloxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran-2 - carbonyl chloride].

A suspension of 5,5' - [(2 - formyloxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H-1 - benzopyran - 2 - carboxylic acid] (100g; 0.2 mole) in 1,2-dichloroethane (2 litres) containing thionyl chloride (100 ml, 1.4 mole) and dimethylformamide was refluxed with stirring for three quarters of an hour after which complete solution was obtained. The solution was filtered hot and the filtrate was evaporated to dryness *in vacuo*. This crude product was crystallized from anhydrous 1,2-dichloroethane (900ml) to give the di-acid chloride as a yellow crystalline solid, (95g), mp 167—170°.

Analysis: Found: C, 54.1; H, 2.6; Cl 12.4%
$C_{24}H_{14}Cl_2O_{10}$ requires: C, 54.1; H, 2.6; Cl 13.3%

Spectral Confirmation

The nmr in deuterochloroform revealed a two proton singlet resonance at 3.0τ for the 3 and 3' protons and also a one proton singlet resonance at 1.8τ for the formyl proton.

(c) 5,5' - [(2 - Hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran - 2-carboxamido)tetrazole].

5-Aminotetrazole (48.5g; 0.57 mole) and 5,5' - [(2 - formyloxytrimethylene)-dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carbonyl chloride] (75g; 0.14 mole) were mutually dissolved in dimethylacetamide (450 ml) and triethylamine (257.5 ml; 1.85 mole). The solution was stirred at room temperature for 18 hours. The mixture was cooled and the triethylamine hydrochloride was filtered off. The filtrate was evaporated to dryness and the resulting yellow solid was triturated with acetone

(800 ml), filtered off and dried *in vacuo* (120g). This solid was suspended in methanol (2,250ml) and concentrated hydrochloric acid (45 ml) and the mixture was refluxed for 1½ hours. The reaction mixture was cooled and the solid was filtered off washed with methanol, ether and finally dried *in vacuo*. This compound was stirred with dimethylformamide (2 litres) at 100° for 1 hour and was then filtered off. This process was repeated. The resulting solid was suspended in benzene (2 litres) and refluxed for 2 hours. The benzene was removed and the solid was refluxed with more benzene (2 litres) for 18 hours. This latter process was repeated once more. The resulting solid was dried at 100° and 0.01 mm for 24 hours to afford pure 5,5'-[(2 - hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole] (56g).

Analysis: Found: C, 49.5; H, 3.3; N, 23.4%
$C_{25}H_{18}N_{10}O_9$: C, 49.8; H, 3.0; N, 23.2%

Spectral Confirmation

The infra red spectrum displayed peaks at 1700 (amide I) cm^{-1}, 1650 (4-oxo) cm^{-1}, 1600 cm^{-1}. The nmr spectrum in hexadeuterodimethylsulphoxide showed a two proton singlet resonance at 3.14τ for the 3 and 3' protons.

(d) 5,5' - [(2 - Hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran-2 - carboxamido)tetrazole]disodium salt.

5,5 - [(2 - Hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran-2 - carboxamido)tetrazole] (6.02g; 0.01 mole) and sodium bicarbonate (1.68g; 0.02 mole) were allowed to react in hot water (400ml). The resulting hot solution was filtered and the filtrate was cooled and diluted with acetone (3 litres). The white precipitate obtained was filtered off and washed with acetone and ether. The product was dried at 100° and 0.001 mm for 18 hours (3.9g).

Analysis: Found: C, 43.1; H, 3.0; N, 20.0%
$C_{25}H_{16}N_{10}Na_2O_9$ with 7.4% water content requires:
C, 43.0; H, 3.14; N, 20.1%

The infra red spectrum displayed peaks at 1690 (amide I) cm^{-1}, 1650 (4-oxo) cm^{-1} and 1600 cm^{-1}. The nmr spectrum in hexadeuterodimethylsulphoxide displayed a two proton singlet resonance at 3.24τ for the 3 and 3' protons.

Example 7.

5,5' - [(2 - Hydroxytrimethylene) - dioxy]bis[1 - benzyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole].

5,5' - [(2 - Formyloxytrimethylene) - dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2-carbonyl chloride] (5.3g) and 5-amino-1-benzyltetrazole (5.25g) were mutually dissolved in dry N,N-dimethylacetamide (50 ml). Triethylamine (2.3 ml) was added and the solution was stirred at 21°C for 18 hours. The mixture was cooled to 0°C and the triethylammonium chloride was filtered off. The filtrate was evaporated to dryness *in vacuo* to give a yellow oil which was triturated with water to give a yellow solid. The solid was filtered off, washed with water and refluxed with methanol (125 ml) and concentrated hydrochloric acid (2 ml) for 1½ hours. The 5,5' - [(2 - hydroxytrimethyl) - dioxy]bis[1 - benzyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole] was filtered off washed with methanol and dried *in vacuo* to give a white powder (5.2 g), mp 225—226°C.

Spectral Confirmation

The nmr spectrum in hexadeuterodimethylsulphoxide revealed a broad, five proton, singlet at 5.65τ for the hydroxytrimethylene chain; a four proton, singlet at 4.40τ for the benzylic methylene groups; a two proton, singlet at 3.24τ for the 3 and 3'-protons; a ten proton, singlet at 2.70τ for the aromatic protons of the benzyl groups and a series of multiplets between 2.9 and 2.2τ for aromatic protons of the chromone moieties.

Example A.

The procedure set out below may be used to assess the effectiveness of a compound in inhibiting the release of the pharmacological mediators of anaphylaxis.

In this test, the effectiveness of the compounds in inhibiting the passive

cutaneous anaphylactic reaction in rats is assessed. It has been proved that this form of test gives reliable qualitative indications of the ability of the compounds under test to inhibit antibody-antigen reactions in man.

In this test method Charles River France/Fisons bred rats (male or female) having a body weight of from 100 to 150 gms are infected subcutaneously at weekly intervals with *N. brasiliensis* larvae in doses increasing from about 2000 larvae per animal to 12000 larvae per animal in order to establish the infection. After 8 weeks the rats are bled by heart puncture and 15—20 mls. of blood collected from each animal. The blood samples are then centrifuged at 3500 rpm. for 30 minutes in order to remove the blood cells from the blood plasms. The serum is collected and used to provide a serum containing *N. brasiliensis* antibody. A pilot sensitivity test is carried out to determine the least quantity of serum required to give a skin weal in control animals in the test described below of 2 cm diameter. It has been found that optimum sensitivity of rats in the body weight range 100—130 is obtained using a serum diluted with eight parts of physiological saline solution. This diluted solution is called antibody serum A.

The antigen to react with the antibody in serum A is prepared by removing *N. brasiliensis* worms from the gut of the infested rats, centrifuging the homogenate and collecting the supernatant liquor. This liquor is diluted with saline to give a protein content of 1 mg/ml and is known as solution B.

Charles River France/Fisons bred rats in the body weight range 100 to 130 gms are sensitised by intradermal injection of 0.1 mls of serum A into the right flank. Sensitivity is allowed to develop for 24 hours and the rats are then injected intravenously with 1 ml/100 gms body weight of a mixture of solution B (0.25 mls), Evans Blue dye solution (0.25 mls) and the solution of the compound under test (0.5 mls varying percentages of active matter). Insoluble compounds are administered as a separate intraperitoneal injection 5 minutes before intravenous administration of solution B and Evans Blue dye. For each percentage level of active matter in the solution under test five rats are injected. Five rats are used as controls in each test. The dosages of the compound under test are selected so as to give a range of inhibition values.

Thirty minutes after injection of solution B the rats are killed and the skins removed and reversed. The intensity of the anaphylactic reaction is assessed by comparing the size of the characteristic blue weal produced by spread of the Evans Blue dye from the sensitisation site, with the size of the weal in the control animals. The size of the weal is rated as 0 (no weal detected, i.e. 100% inhibition) to 4 (no difference in size of weal, i.e. no inhibition) and the percentage inhibition for each dose level calculated as:—

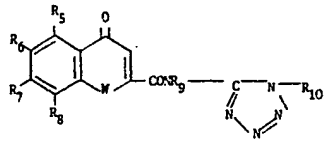
$$\% \text{ inhibition} = \frac{(\text{Control group score} - \text{streated group score}) \times 100}{\text{Control Group score}}$$

The percentage inhibitions for the various dose levels are plotted graphically for each compound. From these graphs the dosage required to achieve a 50% inhibition of the anaphylactic reaction (ID_{50}) may be determined.

The compounds are also evaluated in the above manner using intestinal and gastric administration of the compound.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,

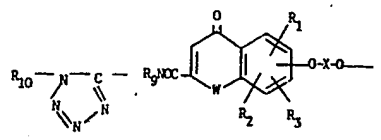


I

in which R_5, R_6, R_7 and R_8, which may be the same or different, each represent hydrogen, alkyl, halogen, hydroxy, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy or phenylalkoxy; the alkyl, alkenyl, phenyl, alkoxy, alkenyloxy and phenylalkoxy groups optionally being substituted by a hydroxy, alkoxy, or halo group or by a heterocyclic ring containing carbon and oxygen,

or an adjacent pair of R_5, R_6, R_7, R_8, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

or one of R_5, R_6, R_7 and R_8 represents a group of formula XXI,



XXI

in which R_1, R_2, and R_3 have the same significances as R_5, R_6, R_7 and R_8 above, save that they do not represent a group of formula XXI and that an adjacent pair of R_1 to R_3 do not, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

X is a saturated or unsaturated, substituted or unsubstituted, straight or branched hydrocarbon chain which may be interrupted by a carbocyclic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups,

each pair of R_9 and R_{10} may be the same or different, and

R_9 and R_{10} are the same or different, and are hydrogen, alkyl C1 to 6, alkenyl C2 to 6, phenyl-(alkyl C1 to 6), alkanoyl C2 to 6 or alkoxy carbonyl C2 to 6, and

W is oxygen or sulphur,

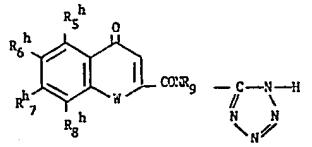
provided that when R_9 and R_{10} are both hydrogen, R_5, R_6, R_7 and R_8 do not represent a group of formula XXI and W is oxygen, then

(i) 3 or 4 of R_5, R_6, R_7 and R_8 are other than hydrogen, or

(ii) at least one of R_5, R_6, R_7 and R_8 represent alkenyl, phenyl or alkenyloxy; or an alkyl, alkenyl, phenyl, alkoxy, alkenyloxy, phenoxyalkoxy or phenylalkoxy group each of which is substituted by a halo group or by a heterocyclic ring containing carbon and oxygen; or an alkyl, alkenyl, phenoxyalkoxy, phenylalkoxy or phenyl group each of which is substituted by a hydroxy or alkoxy group,

or a pharmaceutically acceptable salt thereof, which comprises

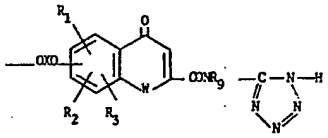
(a) producing a compound of formula Ia,



Ia

in which W and R_9 are as defined above, and

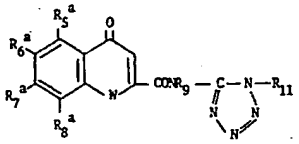
R_5^h, R_6^h, R_7^h and R_8^h have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^h, R_6^h, R_7^h and R_8^h may represent a group of formula XXII,



XXII

in which X, R_1, R_2, R_3, W and R_9 are as defined above,

by replacing a group R_{11} with hydrogen in a compound of formula II,

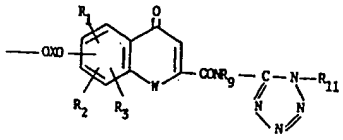


II

in which R_9 and W are as defined above, and

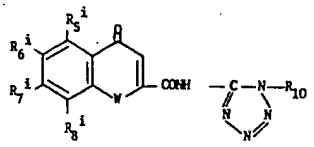
R_{11} represents an aralkyl, an aroylalkyl, an acyl or an amino group, or a group

$-(CH_2)_2G$ is which G is an electron withdrawing group, and
R_5^a, R_6^a, R_7^a and R_8^a have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^a, R_6^a, R_7^a and R_8^a may represent a group of formula III,



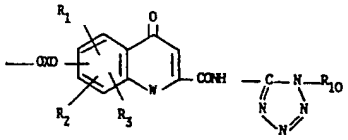
III

in which R_1, R_2, R_3, X, R_9 and R_{11} are as defined above,
(b) producing a compound of formula Ib,



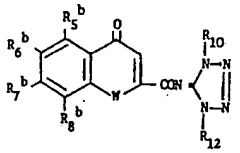
Ib

in which W and R_{10} are as defined above, and
R_5^i, R_6^i, R_7^i and R_8^i have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^i, R_6^i, R_7^i and R_8^i may represent a group of formula XXIII,



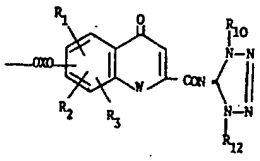
XXIII

in which X, R_1, R_2, R_3, W and R_{10} are as defined above, by
(i) replacing a group R_{12} with a hydrogen in a compound of formula IV,



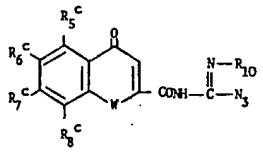
IV

in which W and R_{10} are as defined above,
R_{12} has the same significance as R_{11}, and
R_5^b, R_6^b, R_7^b and R_8^b have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^b, R_6^b, R_7^b and R_8^b may be a group of formula V,



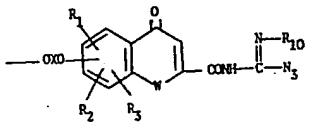
V

in which X, R_1, R_2, R_3, W, R_{10} and R_{12} are as defined above,
(ii) cyclising a compound of formula VI,



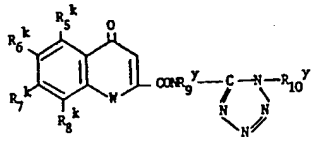
VI

in which W and R_{10} are as defined above, and
R_5^c, R_6^c, R_7^c and R_8^c have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^c, R_6^c, R_7^c and R_8^c may represent a group of formula VII,



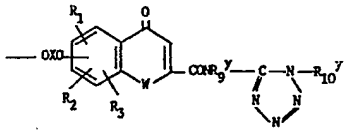
VII

in which X, R_1, R_2, R_3, W and R_{10} are as defined above,
(c) producing a compound of formula Ic,



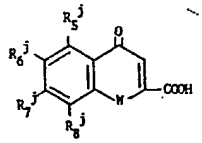
Ic

in which W and the proviso are as defined above,
R_5^k, R_6^k, R_7^k and R_8^k have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^k, R_6^k, R_7^k and R_8^k may represent a group of formula XXV,



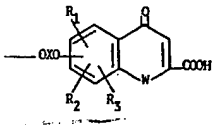
XXV

in which R_1, R_2, R_3, W and X are as defined above, and
R_9^y and R_{10}^y have the same significances as R_9 and R_{10} above, save that R_9^y must be hydrogen when R_{10}^y is hydrogen, by reacting a compound of formula VIII,



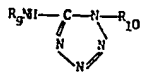
VIII

in which W is as defined above, and
R_5^j, R_6^j, R_7^j and R_8^j have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^j, R_6^j, R_7^j and R_8^j may represent a group of formula XXIV,



XXIV

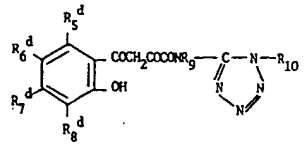
in which X, R_1, R_2, R_3 and W are as defined above,
or an acid halide, an ester or a mixed anhydride thereof, with a compound of formula IX,



IX

in which R_9 and R_{10} are as defined above,

(d) producing a compound of formula I in which W is oxygen by cyclising a compound of formula X,

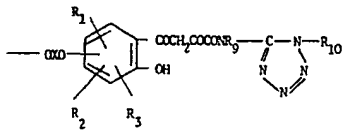


X

or an alkali metal salt thereof,

in which R_9 and R_{10} are as defined above, and

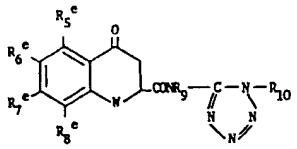
R_5^d, R_6^d, R_7^d and R_8^d have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^d, R_6^d, R_7^d and R_8^d may represent a group of formula XI,



XI

in which R_1, R_2, R_3, X, R_9 and R_{10} are as defined above,

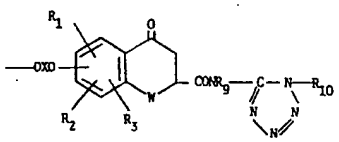
or (e) selectively dehydrogenating a compound of formula XII,



XII

in which W, R_9 and R_{10} are as defined above, and

R_5^e, R_6^e, R_7^e and R_8^e have the same significances as R_5, R_6, R_7 and R_8 above, save that one of R_5^e, R_6^e, R_7^e and R_8^e may represent a group of formula XIII,



XIII

in which R_1, R_2, R_3, X, W, R_9 and R_{10} are as defined above,

and where desired or necessary converting the compound of formula I to a pharmaceutically acceptable salt thereof.

2. A process according to part (a) of Claim 1, wherein R_{11} is an aralkyl group and the reaction comprises catalytic hydrogenation.

3. A process according to part (b)(i) of Claim 1, wherein R_{12} is an aralkyl group.

4. A process according to part (b)(ii) of Claim 1, wherein the cyclisation is carried out under basic conditions or at an elevated temperature.

5. A process according to part (c) of Claim 1, wherein the mixed anhydride is derived from a sulphonic acid, a sterically hindered carboxylic acid or an alkoxy formic acid.

6. A process according to part (c) of Claim 1, wherein the acid halide is an acid chloride.

7. A process according to part (c) of Claim 1 or to Claims 5 or 6, wherein the reaction is carried out in a solvent which will not react with either the compound of formula IX or the mixed anhydride or acid halide.

8. A process according to part (d) of Claim 1, wherein the cyclisation is carried out in the presence of an acid and in a solvent which is inert under the reaction conditions.

9. A process according to part (e) of Claim 1, wherein the dehydrogenation is carried out using a mild oxidising agent or by halogenation followed by dehydrohalogenation.

10. A process for the production of a pharmaceutically acceptable salt of a compound of formula I, as defined in Claim 1, which comprises treating a compound of formula I or another salt thereof, with a compound containing an available pharmaceutically acceptable cation.

11. A process according to Claim 10, which comprises treating a compound of formula I with a base, or with an appropriate salt using a metathetical process.

12. A compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, whenever prepared by a process according to any one of Claims 1 to 11.

13. A compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

14. A compound according to Claim 13, wherein R_5, R_6, R_7 and R_8 each contain less than 8 carbon atoms.

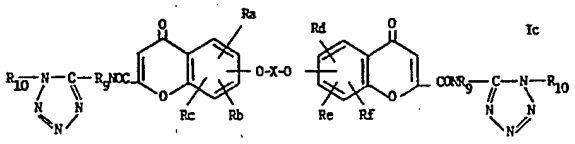
15. A compound according to Claim 13, wherein one of R_5, R_6, R_7 and R_8 represent a group of formula XXI as defined in Claim 1.

16. A compound according to any one of Claims 13 to 15, wherein R_1, R_2, R_3, R_5, R_6, R_7 and R_8 are selected from ethyl, chloro, allyl, ethoxy, allyloxy, benzyloxy, hydroxypropoxy, ethoxy-ethoxy, or alkoxy substituted by a 5 or 6 membered heterocyclic ring containing carbon and oxygen.

17. A compound according to any one of Claims 13 to 16, wherein R_9 and R_{10} are different, one being hydrogen and the other being alkyl Cl to 6 or phenyl-(alkyl Cl to 6).

18. A compound according to any one of Claims 13 to 17, wherein R_9 and R_{10} are selected from hydrogen, methyl, benzyl, allyl, acetyl and ethoxycarbonyl.

19. A compound according to Claim 13 or any one of Claims 15 to 18 of formula Ic,



Ic

in which X, R_9 and R_{10} are as defined in any one of Claims 13 and 16 to 18, and Ra, Rb, Rc, Rd, Re and Rf are the same or are different and each is a hydrogen or halogen atom or an alkyl, hydroxy, alkenyl, alkenyloxy, alkoxy, hydroxyalkoxy or alkoxyalkoxy group.

20. A compound according to Claim 19, wherein not more than one of Ra, Rb and Rc and not more than one of Rd, Re and Rf is other the hydrogen.

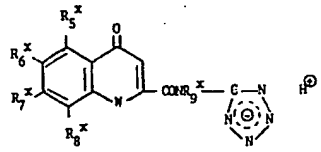
21. A compound according to Claim 19, wherein all of Ra, Rb, Rc, Rd, Re and Rf are hydrogen.

22. A compound according to Claim 13 or any one of Claims 15 to 21, wherein X is an optionally hydroxy substituted straight or branched hydrocarbon chain, which may be interrupted by one or more oxygen atoms, and contains from 3 to 7 carbon atoms.

23. A compound according to Claim 22, wherein X is a $—CH_2CHOHCH_2—$ chain.

24. A compound according to Claim 13 or any one of Claims 15 to 23, wherein the —OXO— group links the 5 and 5'-positions of the chromone nuclei.

25. A compound of formula Id,



Id

in which R_5^x, R_6^x, R_7^x and R_8^x which may be the same or different, each represent hydrogen, alkyl, halogen, hydroxy, alkenyl, phenyl, alkoxy, alkenyloxy

or phenylalkoxy; the alkyl, alkenyl, phenyl, alkoxy, alkenyloxy and phenylalkoxy groups optionally being substituted by a hydroxy, alkoxy or halo group or by a heterocyclic ring containing carbon and oxygen,

or an adjacent pair of R_5, R_6, R_7 and R_8, together with the adjacent carbon atoms in the benzene ring, form a 5 or 6 membered carbocyclic ring,

R_9^x is hydrogen or lower alkyl,

and the proviso is as defined with respect to formula I in Claim 1.

26. 1 - Methyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole.

27. 1 - Benzyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole.

28. 5 - [8 - Allyl - 5 - (3 - methylbutoxy) - 4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole.

29. 5 - [2 - (4 - Chlorophenoxy)ethoxy] - 4 - oxo - 8 - *n* - propyl - 4H - 1 - benzopyran - 2 - carboxamido]tetrazole.

30. 5,5′ - [(2 - Hydroxytrimethylene) - dioxy]bis[5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole].

31. 5,5′ - [(2 - Hydroxytrimethylene) - dioxy]bis[1 - benzyl - 5 - (4 - oxo - 4H - 1 - benzopyran - 2 - carboxamido)tetrazole].

32. A pharmaceutically acceptable salt of a compound according to any one of Claims 13 to 31.

33. A sodium salt of a compound according to any one of Claims 13 to 31.

34. A compound according to any one of Claims 13 to 33 having a particle size of from 0.01 to 10 microns.

35. A pharmaceutical composition comprising a compound according to any one of Claims 13 to 34, as active ingredient, in admixture with a solid or liquid pharmaceutically acceptable diluent or carrier.

36. A composition according to Claim 35 comprising from 0.17 mg to 600 mg of active ingredient in unit dosage form.

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